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November 11, 2005

VIA FEDERAL EXPRESS

Division of Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Comments of Mylan Pharmaceuticals Inc. on Docket No. 2005P-0352: Bioequivalence Criteria for Generic Versions of Ditropan XL® (oxybutynin chloride) Extended Release Tablets

Dear Sir or Madam:

Mylan Pharmaceuticals Inc. ("Mylan") submits these additional comments in opposition to the above-referenced Citizen Petition regarding bioequivalence requirements for generic oxybutynin extended-release products, filed by Ortho-McNeil Pharmaceutical, Inc. ("Ortho-McNeil") on August 29, 2005 (the "Citizen Petition"). Mylan previously submitted comments in opposition to the Citizen Petition on September 30, 2005, in which Mylan provided reasons why the bioequivalence testing proposed by Ortho-McNeil should not delay the approval of Mylan's generic oxybutynin extended-release products. Ortho-McNeil also submitted a supplement to the Citizen Petition on October 7, 2005 (the "Supplement").

Mylan has an interest in the outcome of the Citizen Petition because the petitioner has requested that FDA require generic applicants for extended-release oxybutynin products to conduct additional bioequivalence testing.[1] Specifically, Ortho-McNeil requests FDA to require generic applicants to apply bioequivalence criteria to: (i) both oxybutynin and its major metabolite, desethyloxybutynin; and (ii) separately to the R- and S- enantiomers of both oxybutynin and desethyloxybutynin.

The crux of Ortho-McNeil's argument is that there is nonlinear absorption of either or both enantiomers such that the R/S concentration ratios of the parent and

[1] Based on the data submitted in its application, FDA tentatively approved Mylan's ANDAs for Oxybutynin Chloride Extended-Release Tablets, 5mg and 10mg on January 12, 2005. As noted in Mylan's previous comments, on September 27, 2005, the United States District Court for the Northern District of West Virginia held that Mylan does not infringe Alza Corporation's patent and that the patent is invalid, thus terminating Mylan's 30-month stays.

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metabolite change with drug input rate. Drug input rate, Ortho-McNeil contends, differs among extended-release oxybutynin products. Accordingly, Ortho-McNeil posits that the only way to ensure bioequivalence and true therapeutic equivalence of extended-release oxybutynin products is to conduct the additional bioequivalence studies outlined in the Citizen Petition.

Mylan respectfully submits that no additional bioequivalence requirements are necessary for approval of Mylan's generic oxybutynin extended-release products, and that the Ortho-McNeil Citizen Petition should be denied for the following additional reasons. First, Mylan in its pivotal bioequivalency studies measured both the parent and active metabolite under fasting and fed conditions. Second, Ortho-McNeil does not satisfy all four of the conditions required by FDA Guidance[2] to measure the individual enantiomers. Third Ortho-McNeil's recent actions contradict their position in the Citizen Petition to require the measurement of individual enantiomers. Finally, Ortho-McNeil's competitive interest in the actions requested, which would inevitably delay generic competition warrants a skeptical view of the Citizen Petition.

A. Mylan Agrees with Ortho-McNeil that Oxybutynin's Metabolite, Desethyloxybutynin, Should be Measured in Bioequivalence Studies

As noted in Mylan's original comments to the Citizen Petition, Mylan agrees with Ortho-McNeil that oxybutynin's major metabolite, desethyloxybutynin, meets the criteria for requiring the measurement of an active metabolite to support bioequivalence. As such, in its pivotal bioequivalence studies, Mylan measured both oxybutynin and its active metabolite, desethyloxybutynin under fasting and fed conditions. Ortho-McNeil in its Supplement contends that for certain drugs, like oxybutynin, metabolite data is more than merely supportive evidence in determining bioequivalence.[3] Mylan reiterates FDA Guidance which clearly states that "the metabolite data can be used to provide supportive evidence of comparable therapeutic outcome".[4] FDA Guidance is void of any mention of metabolite data being more than supportive evidence for certain types of drugs. Accordingly, Mylan believes that the Citizen Petition is without merit as far as it applies to the approval of Mylan's ANDAs for Oxybutynin Chloride Extended-Release Tablets, 5mg and 10mg.

B. Ortho-McNeil Fails to Demonstrate the Necessity for Applying Bioequivalence Criteria to the R- and S- Enantiomers of Both Oxybutynin and Desethyloxybutynin

FDA Guidance clearly delineates the circumstances under which bioequivalence criteria should be separately applied to individual enantiomers. The four conditions which must be met to require the individual measurement of enantiomers are: (i) the enantiomers exhibit different pharmacodynamic characteristics; (ii) the enantiomers

[2] FDA Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations. October 2000 ("FDA Guidance") p. 19
[3] Supplement at 2.
[4] FDA Guidance at 19.

exhibit different pharmacokinetic characteristics; (iii) primary efficacy and safety activity resides with the minor enantiomer; and (iv) nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at least one of the enantiomers.[5]

There are very few examples of drug products that meet all four conditions to require the application of bioequivalence criteria to the individual enantiomers. Mylan's original comments addressed the failure of Ortho-McNeil to meet the fourth condition of showing nonlinear absorption of at least one of the enantiomers. Ortho-McNeil criticized Mylan's use of Ditropan XL labeling and comments made by the FDA reviewer in the Summary Basis of Approval (SBA) to demonstrate its position that there is no reason to believe that nonlinear absorption is present. Mylan in these additional comments addresses the weakness of Ortho-McNeil's argument on nonlinear absorption as well as the other conditions required by FDA Guidance to measure the individual enantiomers.

- **Oxybutynin enantiomer(s) exhibits linear absorption.**

Mylan echoes its original comments here and provides additional reasons why Ortho-McNeil's argument that there is nonlinear absorption present is not sufficiently supported. First, Mylan references the Ditropan XL labeling for information provided on a pediatric study conducted by Ortho-McNeil which assumes linear absorption. Second, Ortho-McNeil's application of analysis from a comparison of an immediate-release oxybutynin formulation to an extended-release oxybutynin formulation is not relevant to ranges of inputs anticipated for extended-release oxybutynin formulations which may be shown to be bioequivalent. Third, a closer review of the data relied upon in the Citizen Petition demonstrates that a separate evaluation of the individual enantiomers is not necessary.

First, Ditropan XL labeling provides data on a pediatric study which was conducted with results dose-normalized to an equivalent of Ditropan XL 5mg. The data presented on the individual enantiomers assumes that the enantiomers exhibit dose proportionality across the dosing range investigated (5 to 20mg). If Ortho-McNeil takes the position that absorption of either or both enantiomers is not linear, then the data presented in the labeling for pediatric studies is wrong and is a misrepresentation of Ditropan XL. If dose proportionality is not a proper indicator of linear absorption, then Ortho-McNeil should have reported such results for each dose, for separately measured enantiomers.

Second, the primary data provided by Ortho-McNeil in the Citizen Petition to support its position is based on a comparison of an immediate-release oxybutynin product to Ditropan XL. Fundamental pharmacokinetic (PK) principles advise that comparing an immediate-release formulation to an extended-release formulation is an irrelevant exercise in determining whether two products are bioequivalent. The expected bounds of inputs for delivery rates from an immediate-release formulation are clearly outside of what can be reasonably expected from an extended-release formulation. Instead, if

[5] Id.

Ortho-McNeil's assertion is correct that different input rates can affect the concentration ratio of R- and S- enantiomers for both the parent and active metabolite, then the data should be evaluated over a relevant range of therapeutic inputs. For example, if oxybutynin was delivered in a manner deemed to be bioequivalent to Ditropan XL, it would be within a relevant range of inputs where R/S ratios have been shown to be the same, as further discussed below.

To demonstrate the effect of dose on nonlinear absorption, Ortho-McNeil analyzed R- and S- ratios for oxybutynin and desethyloxybutynin in a study where Ditropan XL was administered at 10 and 20mg doses.[6] Ortho-McNeil interprets the results of the study to indicate that the dose of oxybutynin did not affect absorption of the enantiomers when administered as tablets having the same in vitro and in vivo release rates.[7] Mylan concurs with the results of the study that the dose of oxybutynin did not affect absorption of the enantiomers, however, the release rates of Ditropan XL at 10 and 20mg are not the same. Although the input rates may be similar with respect to %/hr, there is a two-fold difference in input rate based on mg/hr (based on different doses).[8] Accordingly, the study indicates that the statistical evaluation of the pharmacokinetic (PK) results demonstrate that a two-fold difference in "input" had no effect on R/S ratios of oxybutynin and desethyloxybutynin. The study further supports the reasonable inference that there is linear absorption and that the R/S ratio remains the same for both oxybutynin and desethyloxybutynin over clinically relevant ranges of input associated with Ditropan XL. Moreover, bioequivalent formulations based solely on achiral assay of oxybutynin and desethlyoxybutynin should be considered to be therapeutically equivalent.

Third, assuming that comparing an immediate-release oxybutynin formulation to an extended-release oxybutynin formulation is an appropriate assessment for determining whether there is a potential for the enantiomers to exhibit nonlinear absorption, the data presented by Ortho-McNeil does not support their position. Instead, the data presented in the Citizen Petition and discussed below, supports the conclusion that a bioequivalence determination can be made by achiral measurement of oxybutynin and desethyloxybutynin, which represents the total amount of R- and S- present for the respective analyte.[9]

In a study comparing Ditropan XL and an immediate-release formulation in which volunteers were dosed 10mg/day with either once-daily 10mg Ditropan XL or twice-daily 5mg immediate-release oxybutynin, the steady state PK parameters were determined from the observed Day 4 plasma concentration-time data.[10] The data demonstrates that essentially the same estimate of relative bioavailability is determined whether R-enantiomer, S- enantiomer or the total of R+S enantiomers is evaluated. Accordingly,

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[6] Supplement at 15, Table 4 (Study C-96-068).
[7] Id. at 13.
[8] Supplement at 15, Table 4 (note that Treatment C appears to be mislabeled, as text refers to OROS dose.)
[9] Sathyan, G., Chancellor, MB, Gupta, SK. Effect of OROS® controlled-release delivery on the pharmacokinetics and pharmacodynamics of oxybutynin chloride. *Br J Clin Pharmacol* 2001;52:409-417; Supplement at 74-82.
[10] Id.

bioequivalence can be determined using an achiral assay, which serves as assurance that the individual enantiomers of parent or metabolite would be equivalent.

- **Only the R- enantiomers of oxybutynin and desethyloxybutynin are therapeutically relevant for Ditropan XL.**

Although it can be agreed that the different moieties have been shown to possess varying degrees of antimuscarinic and non-receptor mediated antispasmodic effects, Ortho-McNeil attempts to artificially inflate the importance of direct antispasmodic action, particularly by the S-oxybutynin enantiomer. A review of the data presented by Ortho-McNeil in the Citizen Petition shows that S-oxybutynin and S-desethyloxybutynin are significantly less potent than their R-enantiomer counterparts with respect to antimuscarinic activity, which appears to prevail in pharmacologic activity. In fact, the S-enantiomers most likely contribute little to therapeutic activity at the doses of Ditropan XL clinically administered.

While S-enantiomers may be shown to have some pharmacological effects, these only occur at extraordinarily high levels as compared to R-enantiomers. Therefore, the therapeutic effect of Ditropan XL may be attributed mainly to R-oxybutynin and more specifically to R-desethyloxybutynin. Additionally, the theoretical contribution of S-enantiomers to therapeutic effect is exponentially diminished in light of the much greater relative exposure of R-desethyloxybutynin, which represents approximately more than 50% of total exposure of combined R- and S- oxybutynin and desethyloxybutynin.[11]

Additionally, Ortho-McNeil's claim that S-oxybutynin contributes "more to the spasmolytic effects of oxybutynin" is not supported by the study referenced in the Citizen Petition.[12] In the study relied upon by Ortho-McNeil, inhibition of contractile responses to extracellular potassium in isolated guinea pig bladder strips was used as an indicator of antispasmodic activity. Results taken from the study show that all four enantiomers are essentially equipotent in regards to antispasmodic action:[13]

Compound	Inhibition of K^+ induced contraction IC_{50} (μM) mean ± SE
RS-Oxybutynin	2.22 ± 0.47
R-Oxybutynin	3.56 ± 0.83
S-Oxybutynin	4.77 ± 1.93
RS-Desethyloxybutynin	4.08 ± 0.71
R- Desethyloxybutynin	3.64 ± 0.96
S- Desethyloxybutynin	4.39 ± 0.42

[11] Id.

[12] Smith, ER, Wright, SE, Aberg G. Comparison of the antimuscarinic and antispasmodic actions of racemic oxybutynin and desethyloxybutynin and their enantiomers with those of racemic terodiline, *Arzneim. Forsch Drug Res.* 1998;48: 1012-1018; Supplement at 67-73.

[13] Id. at 1016, Table 2; Supplement at 71.

Similar results for R- and S-oxybutynin antispasmolytic activity in isolated guinea pig bladder strips were obtained in an additional study referenced by Ortho-McNeil in the Citizen Petition. [14] The study indicates that both enantiomers have similar antispasmodic actions as the racemic parent compound.[15]

Compound	Inhibition of K^+ induced contraction IC_{50} (μM) mean ± SE
RS-Oxybutynin	11 ± 2
R-Oxybutynin	12 ± 4
S-Oxybutynin	14 ± 2

Both of the studies referenced above (Smith and Kachur) also determined the antimuscarinic actions of oxybutynin and its enantiomers by inhibition of contractile responses to carbachol (a non-specific muscarinic receptor agonist) in isolated guinea pig bladder strips. As shown below, these results suggest that the R-enantiomers are up to >50 times more potent than their S-enantiomer counterparts such that the rank order of antimuscarinic potency of the compounds tested are: R-desethyloxybutynin > RS-oxybutynin > R-oxybutynin > RS-desethyloxybutynin > S-desethyloxybutynin > S-oxybutynin

Compound	Inhibition of carbachol-induced contraction K_b (nM)* [adapted from Smith et al., 1998]
RS-Oxybutynin	1.2
R-Oxybutynin	1.6
S-Oxybutynin	81
RS-Desethyloxybutynin	2.8
R- Desethyloxybutynin	0.91
S- Desethyloxybutynin	49

*estimated by antilog of negative mean pA_2

Compound	Inhibition of carbachol-induced contraction K_b (nM) [from Kachur et al., 1988]
RS-Oxybutynin	42
R-Oxybutynin	21
S-Oxybutynin	557

[14] Kachur, JF, Peterson, JS, Carter, JP. R and S enantiomers of oxybutynin: pharmacological effects in guinea pig bladder and intestine. *J Pharmacol Exp Ther* 1998;247:867-72, Table 1; Supplement at 35-40.
[15] Id.

The greater antimuscarinic potency of R-oxybutynin relative to S-oxybutynin corresponds with a brief reference reporting investigation of S-oxybutynin for urinary incontinence at doses of 360mg/day, which is approximately 50-fold greater than the amount of R-oxybutynin in a therapeutically relevant 15mg dose of Ditropan XL.[16]

In comparing the antispasmodic effects of oxybutynin and desethyloxybutynin to their antimuscarinic actions in these in vitro studies, it may be inferred that R-oxybutynin and R-desethyloxybutynin are over 1000 times more potent with respect to antimuscarinic effects (based comparison of IC50 to Kb) such that the primary mechanism of action contributing to the efficacy of Ditropan XL is the antimuscarinic effect.[17] Furthermore, it has been shown that there is good correlation among the potencies of muscarinic antagonists to inhibit bladder muscle contractions in vitro and intravascular bladder pressure in vivo in the cystometrogram, which is widely used in humans and animals to measure urodynamic parameters associated with bladder dysfunction.[18]

In summary, with regard to pharmacologic activity: (1) S-oxybutynin and S-desethyloxybutynin contribute very little to the action of Ditropan XL. The S-enantiomers are minor with respect to exposure and have little if any contribution to therapeutic activity. (2) R-desethyloxybutynin has the greatest antimuscarinic potency and also the greatest plasma concentrations, therefore overall, oxybutynin's primary efficacy and safety reside with the major enantiomer. (3) Since the R enantiomer has main activity and little significant activity resides in the S enantiomer, achiral measurement of oxybutynin and desethyloxybutynin should only be required.

- **The primary efficacy and safety activity does not reside with the minor enantiomer.**

Ortho-McNeil interprets FDA Guidance to suggest that R-oxybutynin is the minor enantiomer as defined by total systemic exposure relative to that of the S-enantiomer. This is a purposefully narrow interpretation of the guidance. Ortho-McNeil presents evidence on the comparison of R-oxybutynin to S-oxybutynin to show that R-oxybutynin compared to S-oxybutynin is primarily responsible for the anticholinergic effects of oxybutynin that determine both clinical efficacy and safety.[19] Conveniently, Ortho-McNeil does not compare all four enantiomers to determine which enantiomer contributes to the primary efficacy and safety activity.

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[16] Dmochowski R., Improving the tolerability of anticholinergic agents in the treatment of overactive bladder. *Drug Safety* 2005, 28:583-600

[17].Smith, ER, Wright, SE, Aberg G. Comparison of the antimuscarinic and antispasmodic actions of racemic oxybutynin and desethyloxybutynin and their enantiomers with those of racemic terodiline, *Arzneim. Forsch Drug Res.* 1998;48: 1012-1018; Supplement at 67-73.

[18] Noronha-Blob L., Kachur, JF, Enantiomers of oxybutynin: in vitro pharmacological characterization at M1, M2 and M3 muscarinic receptors and in vivo effects on urinary bladder contraction, mydriasis and salivary secretion in guinea pigs, *J. Pharmacol and Expl Ther* 1991, 256:562-7; Supplement at 48-53.

[19] Supplement at 17-18.

As noted above, both Ortho-McNeil and Mylan agree that oxybutynin forms an active metabolite which requires measurement. Since oxybutynin's metabolite, desethyloxybutynin, is required to be measured, the enantiomers of the metabolite must be considered in evaluating which enantiomer has the greatest presence by exposure. By considering the metabolite, it is the R-desethyloxybutynin enantiomer which is present at the greatest amount (approximately >50% of exposure) as defined by AUC and is the single moiety most contributing to therapeutic effect based on activity and exposure. Therefore, contrary to Ortho-McNeil's assertion, the primary efficacy and safety activity does not reside with the minor enantiomer, R-oxybutynin, but rather with the major enantiomer, R-desethyloxybutynin. Ortho-McNeil fails to demonstrate that the primary safety and efficacy resides with the minor enantiomer.

C. Ortho-McNeil's Contentions in the Citizen Petition Contradict the Methodology of A Recent Study Sponsored by Ortho-McNeil to Determine Drug Interaction with Ditropan XL

Ortho-McNeil is scientifically inconsistent in its position to require the separate measurement of the individual enantiomers to determine bioequivalence. In a recent study sponsored by Ortho-McNeil to investigate drug interaction with co-administration of omeprazole, the method for evaluating drug interaction was based on standard bioequivalence criteria which was applied to achiral measurement of oxybutynin and desethyloxybutynin.[20] The study was conducted by some of the same scientists that Ortho-McNeil relies upon in the Citizen Petition to suggest that R- and/or S-enantiomer(s) exhibits nonlinear absorption. If the separate measurement of the enantiomers was so vital to determine the safety and efficacy of oxybutynin, surely when conducting a study to evaluate drug interaction via bioequivalence criteria, the individual enantiomers would have been measured and evaluated separately. This recent Ortho-McNeil sponsored study, however, relied solely upon achiral measurement of oxybutynin and desethyloxybutynin, as Mylan did in its evaluations to determine bioequivalence. As such, no additional bioequivalence requirements should be imposed on Mylan for Ditropan XL.

D. Ortho-McNeil's Competitive Interest in the Actions Requested Warrants a Skeptical View and Immediate Denial of the Citizen Petition

Ortho-McNeil's two "actions requested" have one plain goal: to delay FDA approval of generic competitors. Having lost its court case with Mylan, on the eve of facing generic competition in the U.S. market for Ditropan XL, Ortho-McNeil makes this last-ditch effort to delay Mylan from competing against Ditropan XL by burdening the Agency to have to potentially respond to the Citizen Petition before awarding Mylan final approval for its already tentatively approved ANDAs for Oxybutynin Chloride Extended-Release Tablets, 5mg and 10mg.

[20] Dmochowski R., Effect of the proton pump inhibitor omeprazole on the pharmacokinetics of extended-release formulations of oxybutynin and tolterodine. *J Clin Pharmacol 2005*, 45:961-968.

The Citizen Petition was obviously timed to maximize the potential impact on the final approval of Mylan's ANDAs. Ortho-McNeil has been aware for years of Mylan's applications for generic version of Ditropan XL, yet has raised this alleged concern only now that it has run out of other ways of blocking competition from Mylan's product.

Ortho-McNeil asks FDA to require generic applicants to separately apply bioequivalence criteria to the R- and S- enantiomers of both oxybutynin and desethyloxybutynin to ensure bioequivalence and true therapeutic equivalence of extended-release oxybutynin products. Despite the fact that Ortho-McNeil's position is based upon an evaluation of an immediate-release oxybutynin formulation to Ditropan XL that "signals" the potential for differences among extended-release oxybutynin products, the petitioner's rationale for requiring additional bioequivalence requirements is moot as clinical data reveals that there is no superiority of Ditropan XL relative to an immediate-release oxybutynin formulation.[21]

In fact, in a memorandum from FDA Group Leader, Marianne Mann, MD, the following was documented: "[c]laims of superiority regarding dry mouth for the XL formulation [relative to the immediate-release formulation] are not supported by the data in this application. Numerous deficiencies need to be addressed in future clinical trials in order to adequately support a superiority claim regarding dry mouth. . . ".[22]

Because Ortho-McNeil's Citizen Petition is nothing more than a transparent attempt to interfere with Mylan's introduction of generic versions of Ditropan XL, regardless of the ultimate outcome of the Citizen Petition, there is no reason that the Citizen Petition should delay approval of Mylan's already tentatively approved ANDAs for Oxybutynin Chloride Extended-Release Tablets, 5mg and 10mg.

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[21] SBA, Administrative Documents, Group Leader Memorandum dated December 14, 1998, by Marianne Mann, MD, section III (www.fda.gov.cder/foi/nda/98/20897).
[22] Id.

Conclusion

For all of the foregoing reasons, the final approval of Mylan's ANDAs should not be delayed regardless of when and/or how the Agency ultimately decides Ortho-McNeil's Citizen Petition.

Respectfully submitted,

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cc: Elizabeth Dickinson, *Office of Chief Counsel (via e-mail)*
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